4. Epidemiology, Disease Transmission & Immunization

4.1 Epidemiological Methods

1-Epidemiology
2-Incidence
3-Prevalance
- Relationship between Prevalence & Incidence

4-Epidemiological Methods
5-Descriptive Epidemiology
- Epidemic
- Types of epidemic
- Propagated epidemic

6-Analytical Epidemiology
- Case Control Study
- Cohart study
- Difference between case control study & cohart study

7- Experimental epidemiology
- Randomized control trial

8- Meta- Analysis
9- Bias
10- Blinding
11- Confounding
12- Matching
13- Association & Causation
14- Uses of Epidemiology

4.2 Disease Transmission in Infectious Diseases

1. **Disease Control/ Elimination / Eradication**
2. **Source & Reservoir**
3. **Cases**
   - **Primary case**
   - **Index case**
   - **Serial interval**
4. **Carriers**
   - **Convalescent carriers**
5. **Disease Transmission**
6. **Incubation period**
   - **Generation time**
7. **Isolation**
8. **Quarantine**
9. **Emporiatrics**
10. **Disinfection**

4.3 Immunization & Cold Chain

1. **Vaccine**
2. **BCG vaccine**
3. **Measles Vaccine**
4. **DPT vaccine**
5. **Inactivated Polio Vaccine (IPV)**
6. **Oral Polio Vaccine (OPV)**
7. **Herd immunity**
8. **Rota Virus Vaccine**
9. **Mycobacterium Indicus Pranii (MIP) vaccine**
10. **Cold Chain**
    - **Vaccine Vial Monitor (VVM)**
11. **National Immunization Schedule(NIS)**
12. **Age limits for delayed immunization in NIS, India**
13. **Adverse Events Following Immunization (AEFI)**
14. **Open Vial Policy**
15. **Mission Indradhanush**

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14- Uses of Epidemiology
15- International Death Certificate (IDC)

1-Epidemiology

- **Definition**- Study of distribution & determinants of health related events in specified populations & the application of this study to the control of health problems
- **3 components**
  - **Frequency of disease**- Prevalance rate, incidence rate
  - **Distribution of disease**- wrt. Time place & person
  - **Determinants of disease**- Identifying the underlying cause or risk factors of disease
- **In epidemiology-**
  - Unit of study is population
  - Concerned with disease pattern in the entire population
  - Interested in relationship between cases & population
  - Seeks to identify source of infection , mode of spread & etiological factor
  - Data from epidemiological studies is symbolized in the form of tables & graphs
- **Measurement of epidemiology**
  - Measurement of distribution of disease
  - Measurement of distribution of factors causing the disease
  - Measurement of needs & utilization of health services
  - Measurement of demographic variables
  - **Measurement of morbidity**- Incidence rate, Prevalence rate etc.
  - **Measurement of mortality-** crude death rate, case fatality rate, proportional mortality rate etc.

Measurements in epidemiology

- **Rate-** numerator is a part of denominator & multiplier is 1000 or 10000 0r 100000 or so on
- **Ratio-** ***numerator is not a part of denominator & both numerator & denominator are unrelated***
  - ***it is expressed as a number***
- **Proportion –** numerator is a part of denominator & multiplier is 100
  - Proportion is always expressed in percentage

Measurement of morbidity

i. **Incidence -** Number of new cases occurring in a defined population during a specified period of time
ii. **Prevalance-** Refers to all current cases (old + new) existing at a given point in time or over a period of time in a given population

Measurement of mortality

1. **Crude death rate** (India- 6.7 per 1000 midyear population)

$$\text{CDR} = \frac{\text{number of death in an area in a year}}{\text{Total midyear population}} \times 1000$$

- ***Midyear population is the population assessed on 1st of July***

2. **Case fatality rate**

$$\textit{CFR} = \frac{\text{total number of death due to a particular disease}}{\text{total number of cases due to the same disease}} \times 100$$

- ***Represents*** the killing power of a disease or ***virulence of the organism***
- ***Better indicator of severity of an acute disease***
- Limitation is that time interval is not specified (***So it's a killing power of a disease with no time interval)***
- Compliments **Survival Rate**

$$\textit{SR} = \frac{\text{total number of patient alive after 5 years}}{\text{Total number of patients diagnosed /treated}} \times 100$$

SR = 1 – CFR (here CFR is taken in decimals i.e. 25% taken as 0.25)

- Describes prognosis
- Useful in cancer studies
- ***Assess standards of therapies***
- ***Whenever screening test is performed – higher 5 year survival rate is observed, this is a potential bias due to earlier diagnosis being made(& not because people live longer)***

3. **Proportional mortality rate**

$$PMR = \frac{\text{number of death from specific disease in a year}}{\text{Total death from all causes in that year}} \times 100$$

- ***Simplest measure of estimating the burden of a disease in the community***
- ***PMR is a proportion***

2-Incidence

- Number of new cases occurring in a defined population during a specified period of time

$$\text{Incidence} = \frac{\text{number of new cases of specific disease during a given time period}}{\text{Population at risk during that period}} \times 1000$$

- ***Incidence is rate***, expressed per 1000
- ***Not influenced by duration of disease***
- Use of incidence is generally restricted to acute conditions
- Incidence can be determined by Cohart study
- ***Incidence is a probability that a healthy individual will develop the disease during specified period***
- ***Incidence measures the absolute risk of developing the disease***
- ***Incidence decreases if a particular programme is efficient***

Special incidence rates

1. ***Attack rate***
   - used when population is exposed for small interval of time e.g. epidemic
   - reflects extent of epidemic

$$\text{Attack rate} = \frac{\text{number of new cases of a specified disease during a specified time interval}}{\text{Total population at risk during the same interval}} \times 100$$

2. ***Secondary attack rate***
   - ***Number of exposed persons developing the disease within the range of the incubation period following exposure to a primary case***
   - ***Denominator includes only those susceptible in close contact***
   - ***If SAR of a disease is more than it means that the disease is more infectious***
   - ***SAR is an index of communicability***
   - Primary case is always excluded both from numerator & denominator for SAR calculation

$$SAR = \frac{\text{number of exposed persons developing disease within a range of IP}}{\text{Total number of exposed susceptible contacts}} \times 100$$

	SAR
Small pox	30-45%
Measles	> 80%
Chicken pox	*90%*
Mumps	86%
Pertussis	90%

Uses of Incidence rate

- For research into aetiology & pathogenesis, distribution of diseases & efficiency of preventive
- therapeutic measures
- If the incidence rate is increasing it indicate ineffectiveness of the current control programmes
- ***Better indicator of efficacy of hospital services & health programs***
- Best measure of disease frequency in etiological studies

3-Prevalance

- Refers to all current cases (old + new) existing at a given point in time or over a period of time in a given population
- Prevalence can be determined by cross sectional study
- ***Prevalence is a proportion*** & not a ratio
- Always expressed in percentage

- Two types-

i. Point Prevalence

Point Prevalance = number of all current cases (old + new) of a specified disease existing at a given point in time x 100
Estimated population at the same point in time

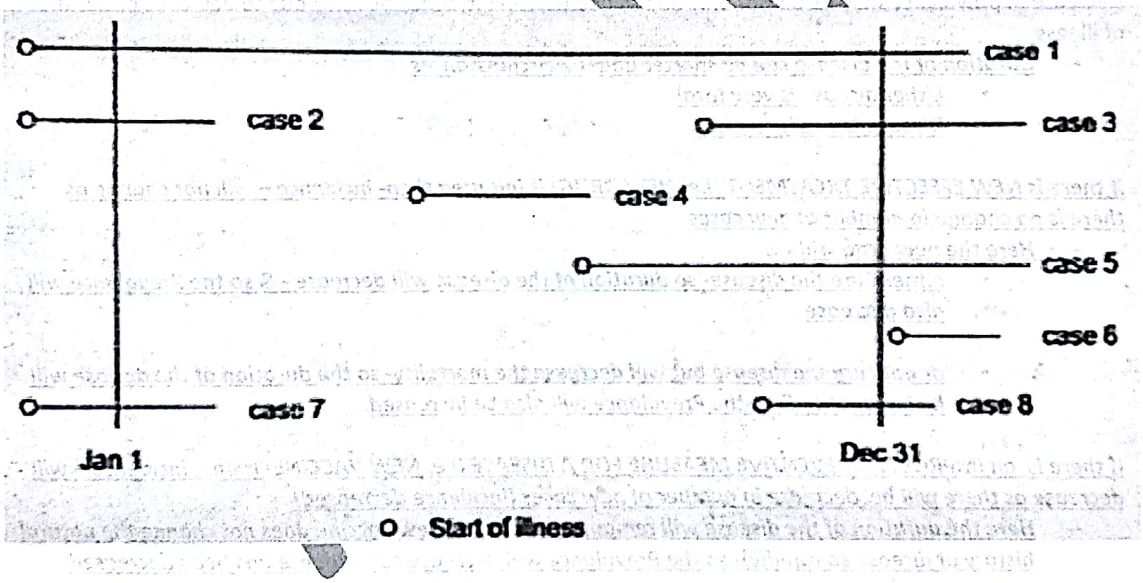
- ***When term Prevalence rate is used , without any further qualification, it is taken to mean point prevalence***

ii. Period Prevalence

Period Prevalance = number of existing cases (old + new) of a specified disease during a given period of time interval x 100
Estimated mid interval population at risk

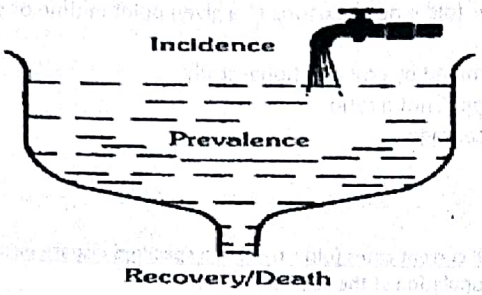
- **Uses of prevalence**
  - To estimate magnitude of disease in the community & identify high risk population

Example of Incidence & Prevalance



- **Incidence** would include - cases- 3, 4, 5 & 8
- **Point Prevalance** (Jan 1)- cases- 1, 2 & 7
- **Point Prevalance** (Dec 31)- cases- 1, 3, 5 & 8
- **Period Prevalance** (Jan - Dec)- cases- 1, 2, 3, 4, 5, 7 & 8

3.1 Relationship between Prevalence & Incidence



- Assuming that the population is stable & incidence & prevalence is unchanging
  Prevalence **= Incidence x Duration of the disease**

  P = I x D
  - Incidence reflects causal factor
  - Duration reflects prognostic factor

- ***Prevalance describes the balance between incidence, mortality & recovery***
- ***Longer the duration of the disease, greater is its prevalence(chronic diseases i.e. neither curable diseases nor rapidly fatal)***
- Decrease in prevalence may result not only due to decrease in incidence but also due to decrease of duration of illness
  - ***Duration of the disease can be shorter under 2 circumstances***
    - ***Either disease is very fatal***
    - ***Disease is easily curable***

- ***If there is NEW EFFECTIVE TREATMENT (i.e. NEW DRUG) is initiated then- incidence – will not change as there is no change in number of new cases***
  - ***Here the new drug will***
    - ***either Cure the disease- so duration of the disease will decrease - & so the Prevalance will also decrease***
    - ***or not cure the disease but will decrease the mortality- so the duration of the disease will be increased - & so the Prevalance will also be increased***

- ***If there is an IMPROVED PREVENTIVE MEASURE FOR A DISEASE (i.e. NEW VACCINE) then - incidence – will decrease as there will be decrease in number of new cases (incidence decreased)***
  - ***Here the duration of the disease will remain the same(as new vaccine does not change the natural history of disease so rapidly)- so the Prevalance will decrease as incidence has been decreased***

- ***If the DISEASE IS MORE FATAL than the duration of disease will decrease & hence the Prevalance will also decrease***

4-Epidemiological Methods

Types of Epidemiological Studies

I. **Observational studies**

1) ***Descriptive studies (hypothesis formulation)***

2) ***Analytical studies (hypothesis testing)***

i. ***Ecological*** / Correlational study (***unit of study is population***)

ii. ***Crossectional/*** prevalence survey/ snapshot of population survey (***unit of study is individual***)

iii. ***Case control*** (***unit of study is individual***)

iv. **Case series study**

v. **Nested case control study**

vi. ***Cohort (unit of study is individual)***

- Prospective cohart
- Retrospective cohart
- Mixed cohart/ combined prospective retrospective cohart

II. ***Experimental studies (hypothesis confirmation)***

1) ***RCT (unit of study is patients***/ cases)
2) ***Field trials*** (***unit of study is healthy people***)
3) ***Community trials*** (unit of study is community)
4) Clinical trial (unit of study is patients/ cases)

❖ ***Migration study- used to study environmental & genetic factors in a disease in population***

❖ ***KAP (knowledge Attitude Practice) study was first used in India to study family planning***

Sequence of studies in epidemiology

Descriptive study → Analytical study → Experimental study

Utilities of epidemiological studies for establishing causality

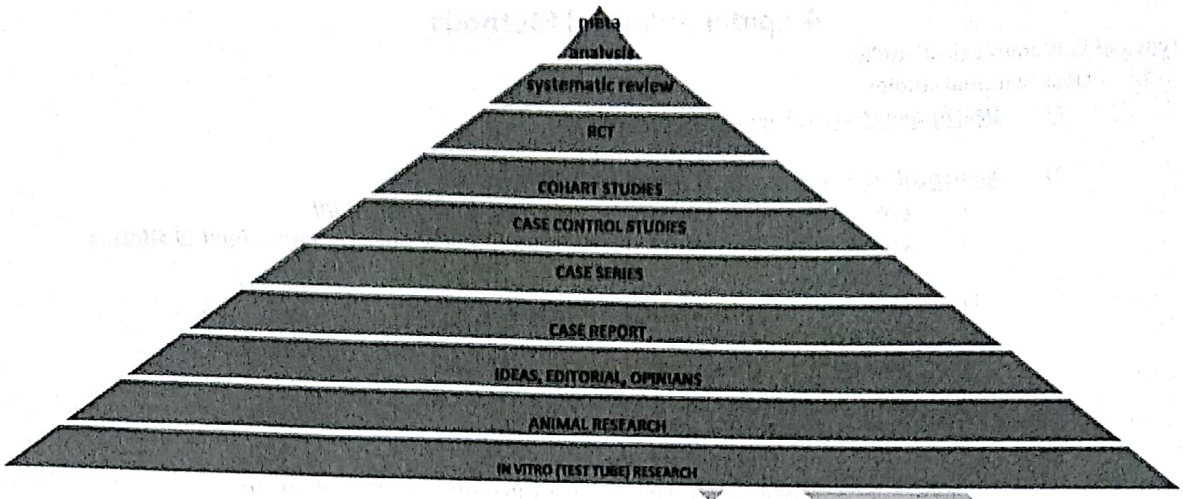
Metaanalysis (strongest) > ***RCT*** > ***Cohart*** (retrospective > prospective) > case control study > crossectional study > ***ecological study (weakest)***

Evidence Based Medicine (EBM)

- ***EBM refers to use of various research findings for taking decisions about best patient care***
- ***Aim is to apply best available evidence gained from scientific method to clinical decision making***
- Gold standard for clinical practice
- ***Father of Evidenced based medicine- David Sackett***
- Statistical parameters used – likelihood ratios & receiver operator characteristic curve

- ***Highest importance is given to strongest epidemiological studies***
  - ***Most important - Metaanalysis , systematic review & blind trials***
  - Highest importance is given to meta-analysis

- Evidence based pyramid
  - **Meta analysis-** highest clinical relevance/ gold standard
  - **In vitro / test tube research** – lowest clinical relevance



5-Descriptive Epidemiology

Descriptive studies

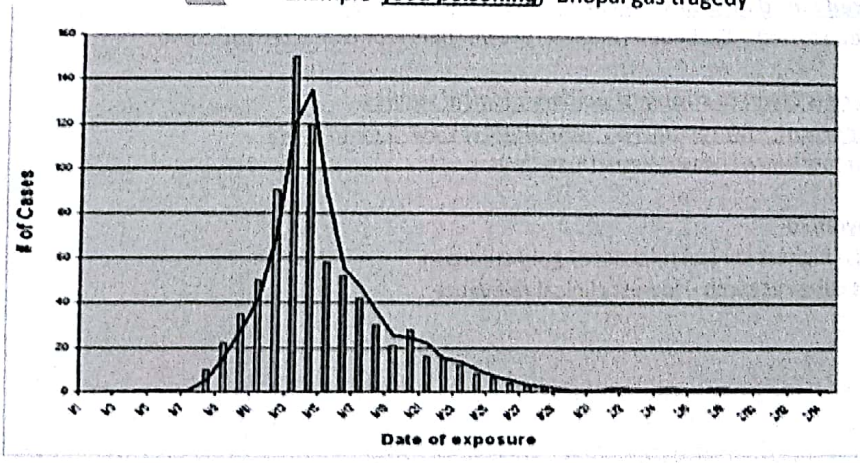
- ***Studying distribution of disease or health related characteristics in human population & identifying the characteristics with which disease seems to be associated***
- ***Best study for assessment of unknown or new disease with no etiological hypothesis***

Procedures in descriptive studies

1. Defining the population to be studied
2. Defining the disease under study
3. ***Describing the disease by Time, Place & Person***
4. Comparing with known indices
5. Formulation of hypothesis

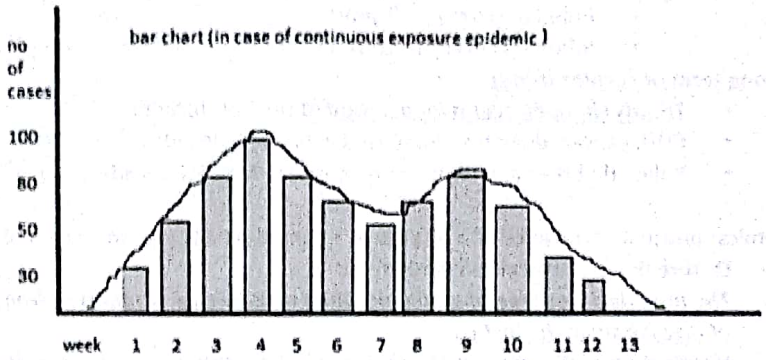
Time distribution

I. **Short term fluctuation** (Epidemics)
   1. **Common source epidemics**
      i. **Single exposure or *point source epidemics***
         - ***Explosive***
         - ***Sharp rise & sharp fall in no. of cases***
         - ***Clustering of cases in a narrow interval of time***
         - ***All case develop within one incubation period of the disease***
         - ***Uniform curve with No secondary waves***
         - Example- ***food poisoning***, Bhopal gas tragedy



II. ***Continuous*** **or repeated or multiple** ***exposure epidemics***

- Sharp rise in number of cases
- Fall in number of cases is interrupted by secondary waves/peaks
- Example- STD-prostitutes, ***contaminated well in a village***, , legionnaire disease outbreak in Philadelphia (1976)



2. **Propagated epidemics-**

- Gradual rise & gradual fall over a long period of time (tail off over a much longer period of time)
- Results from person to person transmission
- Transmission continues till no susceptibles are left or susceptible are no longer are exposed to infected individuals
- Speed of spread depends on herd immunity & secondary attack rate
- Example- HIV, TB, Polio, Hepatitis A

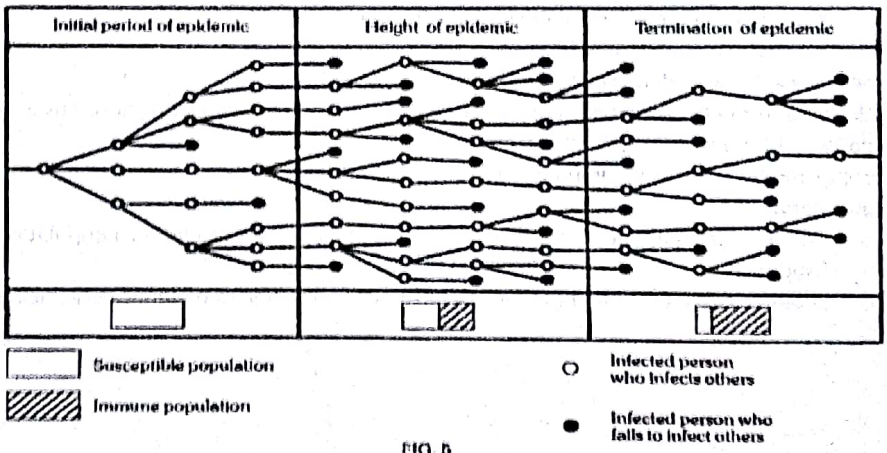
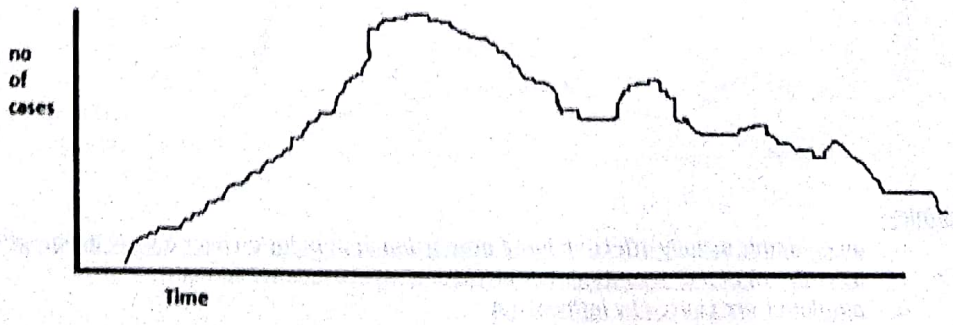


FIG. 5
Course of typical propagated epidemic (Source 4)



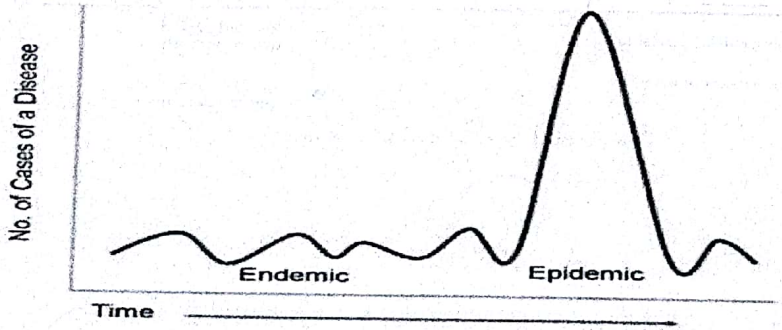
II. **Periodic fluctuation**
   1. ***Seasonal trend***
      - ***It is a seasonal variation of a disease occurrence may be related to environmental conditions***
      - URI infection- winter season
      - GIT infection – summer season
   2. **Cyclical trend**
      - Rubella – every 6 - 9 years
      - Influenza- every 7- 10 years

III. **Long term or *secular trends***
   - ***Trends changes over a long period of*** time or decades
   - CHD, cancer, diabetes - increased in last few decades
   - Polio , diphtheria, typhoid – decreased in last few decades

- **Epidemics**- unusual occurrence of a disease in a community, clearly in excess of expected occurrence
  - **Outbreak** – small localized epidemic
  - ***The area declared free of epidemic when no new case is reported from twice the incubation period of disease since the last case***
  - ***Verification of diagnosis is the first step in investigation o an epidemic***

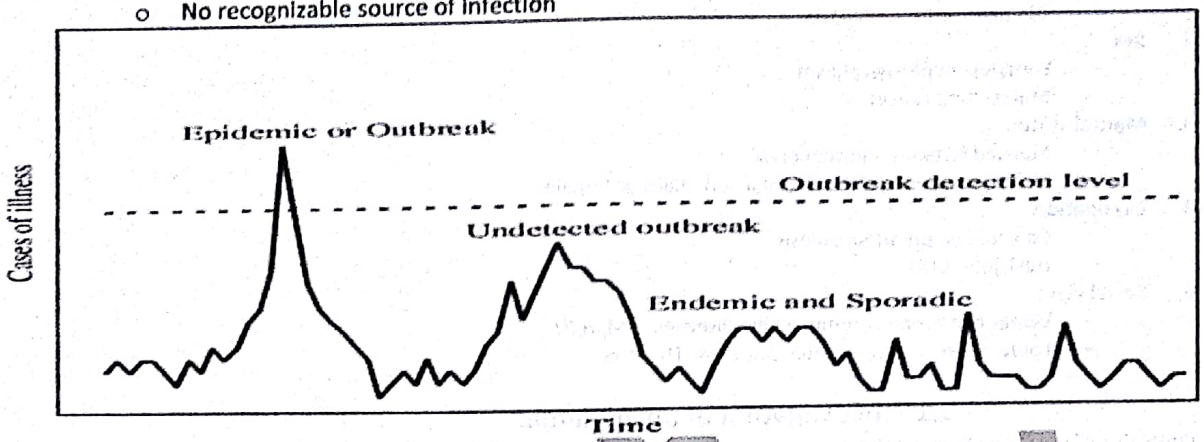
- ***Endemic***
  - ***constant presence*** or usual or expected frequency ***of a disease within a given geographic area***
    a. **Hyper-endemic –**
       - Constant presence of disease at high incidence/prevalence
       - affects all age group

    b. **Holo-endemic –**
       - High level of infection beginning early in life
       - affecting mostly children
  - for the disease to be endemic in a steady state - **R0 x S = 1**
    RO = basic reproduction number of an infection (number of secondary case caused by a single case in a population with no immunity & intervention)
    S = proportion of susceptibles in population
  - **Endemic curve**
    - it's not a straight line as number of cases for the endemic disease in a population will not be fixed throughout a year but it will show seasonal variations
    - Endemic curve & epidemic curve are different as baseline of endemic curve never touches zero



- ***Pandemic –***
  - ***an epidemic usually affecting large proportion of population over a wide geographic area such as entire nation or a continent or world*** (country to country spread)
  - ***pandemic are caused by influenza A***

- ***Sporadic-***
  - Scattered cases, widely separated in space & time & show no connection with each other
  - ***Occurrence of disease in haphazard or irregular pattern***
  - No recognizable source of infection



- **Ecdemic** - disease that originates outside of the area in which it occurs
- ***Exotic disease- disease imported in a country which was not otherwise preseent***

Place distribution

1. ***Local variation***
   - ***Spot maps***
   - Shaded maps

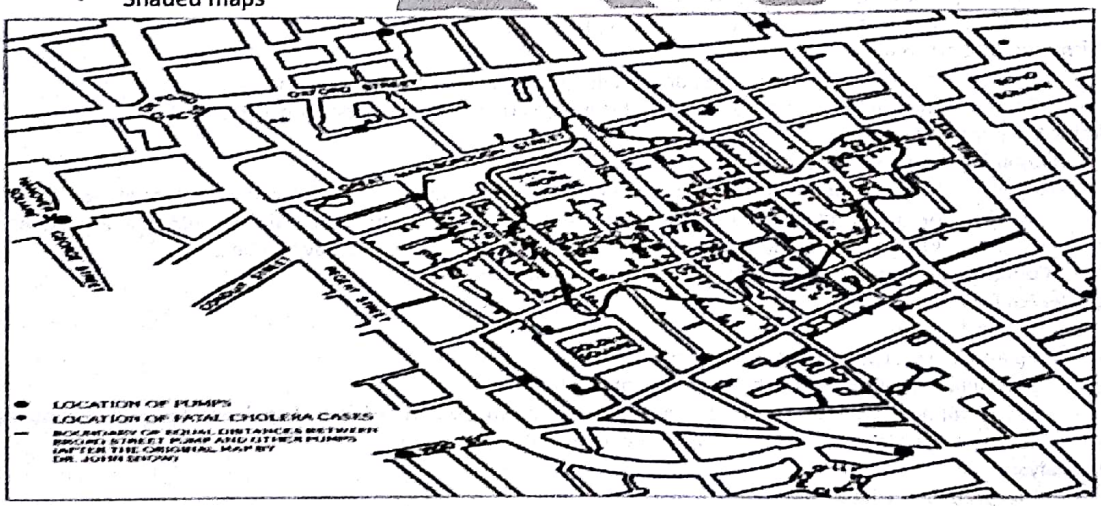


FIG. 6
Spot map of Asiatic cholera in London

2. **Rural – urban variation**
   - **Rural-** Zoonotic diseases, soil transmitted helminths
   - **Urban-** Accidents, CVD
3. **National variation**
   - Northern region- goiter
   - Southern region – malaria
   - Central region- lathyrism
4. **International variation**
   - Japan- Cancer stomach
   - India- Cancer in oral cavity

Person distribution

1. **Age**
   - **Childhood-** measles
   - **Middle age-** cancer
   - **Old age –** atherosclerosis
2. **Sex**
   - **Females-** hyperthyroidism
   - **Males-** lung cancer
3. **Marital status**
   - Married females- cancer cervix
   - Mortality rates are lower in married males or females
4. **Occupation**
   - Coal mines- pneumoconiosis
   - Desk job- CHD
5. **Social class**
   - **Upper class-** non communicable diseases- DM, HTN
   - **Lower class-** communicable diseases- TB, AIDS

5.1 - Investigation of an Epidemic

- **Objective of epidemic investigations**
  - To define magnitude of the epidemic
  - To determine factors responsible for occurrence of epidemic
  - To identify source of infection & modes of transmission
  - To make recommendations to prevent recurrence

1. **Verification of diagnosis**
   - Lab investigations to confirm the diagnosis
   - First step in investigation of an epidemic
   - Not necessary to examine all cases, take sample
2. **Confirmation of epidemic**
   - Done by comparing the disease frequencies during the same period of previous years
   - **Epidemic threshold-** an arbitrary limit of 2 standard errors from the endemic occurrence
3. **Defining the population at risk**
   i. **Obtaining the map of the area**
      - Should contain information concerning natural landmarks, roads & location of all dwellings
      - Area may be divided into segments, using landmarks & may again be divided into smaller sections.
      - Within each sections dwelling units (houses) may be designated by numbers

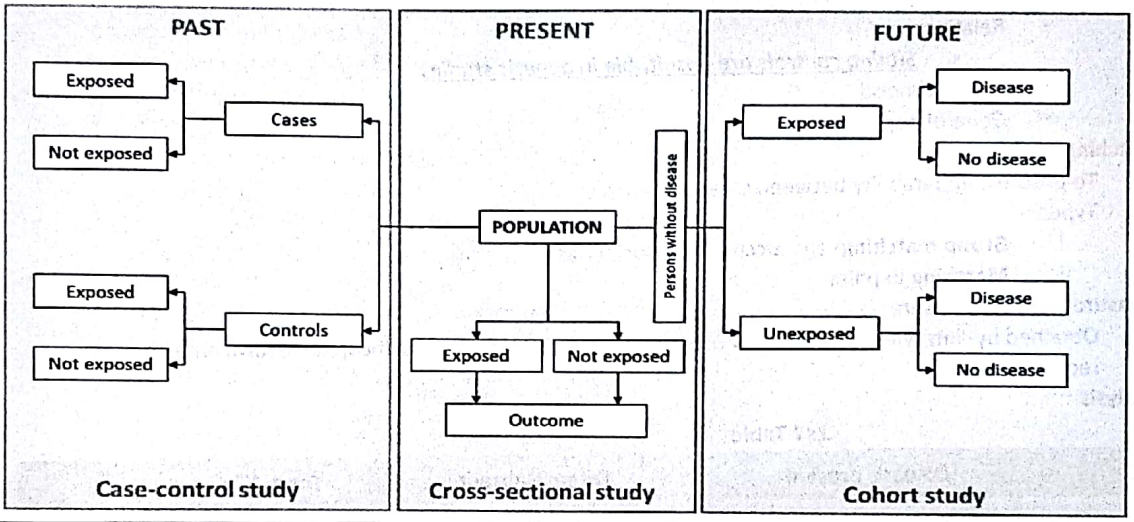
   ii. **Counting the population-** Carried out by house to house v visits
4. **Rapid search for all cases**
   - Medical survey
   - Epidemiological case sheet/ case interview form
   - Searching for more cases at home, family or neighborhood
   - Search for new cases are carried out everyday , till the area is declared free of epidemic, this period is usually taken as twice the incubation period of the occurrence of last case
5. **Data analysis**
   - Analyzed on the basis of
   - **Time-** construct an epidemic curve
   - **Place –** prepare a spot map
   - **Person –** analyze data by age, sex, occupation & other risk factors
6. **Formulation of hypothesis-** To explain possible source, causative agent , modes of spread & environmental factors
7. **Testing of hypothesis-** By comparing the attack rates
8. **Evaluation of ecological factors**
   - Water & milk supply
   - Relate disease with environmental factors to find reservoir of infection & modes of transmission
9. **Further investigation of population at risk-** Medical examination, screening test, examination of suspected sample & biochemical studies
10. **Writing the report**
    - Should be complete & convincing
    - Under following headings- background, historical data, methodology, analysis of data & control measures

6-Analytical Epidemiology

- To determine whether or not a statistical association exists between a disease & suspected factor(exposure)

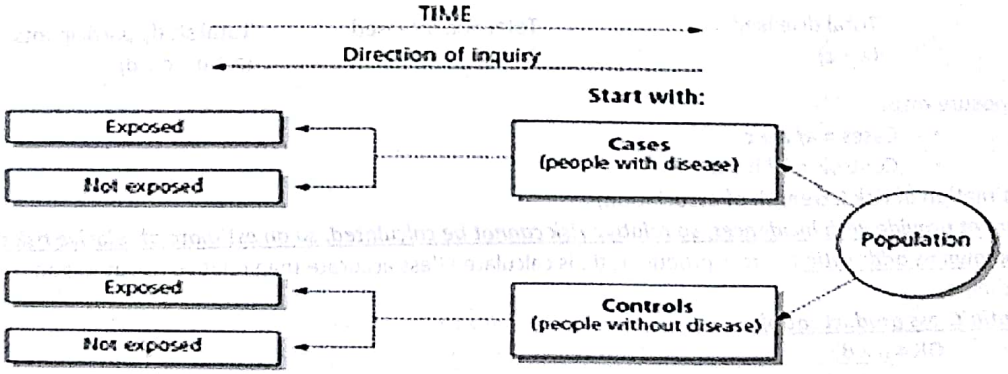
Analytical studies (hypothesis testing)

1. Ecological/ Correlational study (unit of study is population)
2. Crossectional/ prevalence survey/ snapshot of population survey
3. ***Case control study***
4. Case series study
5. Nested case control study
6. Cohort study
   - i. Prospective cohart
   - ii. Retrospective cohart
   - iii. Mixed cohart/ combined prospective retrospective cohart



6.1- Case Control Study

(Retrospective studies/ TROHOC Study/ Backward looking study / effect to cause study/ outcome to exposure study/ disease to risk factor study)



Features

- ***Both exposure & outcome have occurred before the start of study***
- ***Study proceeds backward from effect to cause***
- Uses a control group to support an inference

Steps

1.1. Selection of cases

- **Definition of case**
  - Diagnostic criteria
  - Eligibility criteria
- **Sources of cases**
  - Hospitals
  - General population

1.2 Selection of controls

- Controls must be as similar to the cases as possible , except for the absence of disease
- If study group is small choose up to 4 controls per case(1:4) & in larger studies 1: 1 of cases & controls should be taken
- **Sources of controls-**
  - Hospital (often source of selection bias)
  - Relatives
    - ***Sibling controls are unsuitable in genetic studies***
  - Neighborhood
  - General population

2. Matching

- To ensure comparability between cases & controls
- Types-
  i. **Group matching-** age, occupation, social class
  ii. **Matching in pairs**

3. Measurement of exposure

- Obtained by- interviews, by questionnaire, or by studying past records(hospital record, employment record)

4. Analysis

2×2 Table

	Disease present	Disease absent	Total
Exposure present	Exposed & developed disease (a)	Exposed but not developed disease(b)	Total exposed(a + b)
Exposure absent	Not exposed but developed disease(c)	Neither exposed nor developed disease(d)	Total non exposed(c + d)
Total	Total diseased (a + c)	Total non diseased (b + d)	Total study participants (a + b + c + d)

I. **Exposure rates**
   - Cases = a/ a + c
   - Controls = b/ b + d

II. **Estimation of risk (strength of association)**

- ***Cannot provide with incidences, so relative risk cannot be calculated, so an estimate of relative risk that is known as odds ratio*** or cross product ratio is calculated (less accurate than relative risk as it is an estimate)

Odds ratio(Cross product ratio)

$$OR = \frac{a \times d}{b \times c}$$

- Interpretation- Exposed showed a risk of having disease _____ times that of non exposed
- Indicator of increased risk of disease in predisposed population
- ***It is just an estimate of relative risk not the calculation of relative risk***
- ***Similar to relative risk***

- **OR > 1-** Positive association
  - so many times odds that cases were exposed to a risk factor is more to the odds that the controls were exposed
  - example- OCPs & thromboembolism
- ***OR = 1- No association***
  - Odds that cases were exposed to a risk factor is same as the odds that the controls were exposed
  - Example- smoking & HIV/ AIDS
- **OR < 1-** Negative association
  - So many times odds that cases were exposed to risk factor is less than the odds that the control were exposed
  - Example- regular physical exercise- CHD

Utilities of Case Control Study

- investigation of rare disease
- study of multiple exposure
- investigation of long latent period

Advantages of case control studies

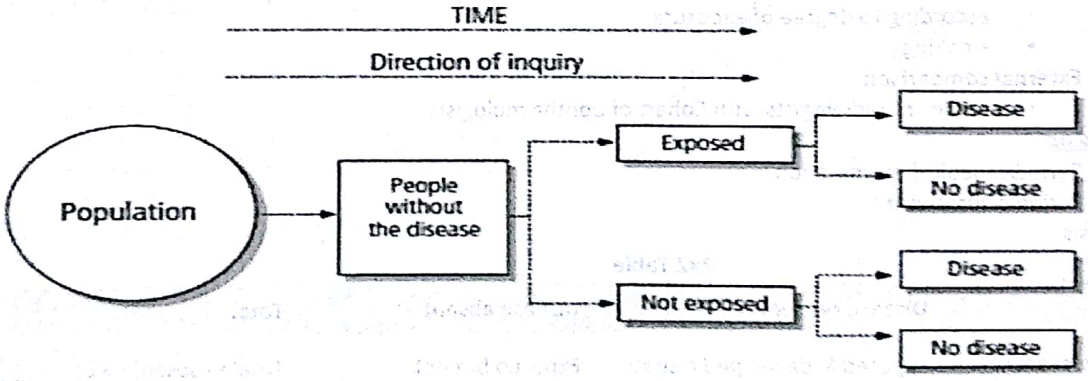
- Rapid & ***inexpensive***
- ***Suitable to investigate RARE DISEASE***
- Risk factors can be identified
  - ***Study multiple potential risk factors of disease***
- ***No ethical problem***

Disadvantages of case control studies

- Selection of appropriate controls may be difficult
- ***Problem of selection bias***
- ***Incidence cannot be measured***

6.2- Cohort Study

(Prospective study/ Longitudinal study/ Incidence study/ Forward looking study/ case to effect study/ exposure to outcome study/ risk factor to disease study/ follow-up study)



TYPES

1. **Prospective cohart studies**
   - **Current cohart studies / *Concurrent cohart studies***
   - Outcome has not yet occurred when the study has begun, only exposure has occurred , we look for development of some disease in both exposed & non exposed groups
   - Ex - Framingham heart study
   - **Retrospective cohart studies**

2. **Retrospective cohart studies**
   - **Historical cohart studies / *Non-concurrent cohart studies***
   - Both exposure as well as outcome have occurred, first we go back in time & take only exposure into consideration then look for development of same disease in both exposed & non exposed
   - Ex- Effect of fetal monitoring on neonatal deaths
   - Example- ***a cohart of nurses with control group is studied for use of IUD & abdominal pain as side effect , in case control manner***
3. **Combined Retrospective Prospective cohart studies**
   - **Mixed cohart study**
   - First we go back in time & take only exposure into consideration , later cohart is followed prospectively into future for outcome
   - Ex- Court Brown & Doll study on effect of radiation therapy

Features

- ***Cohorts are identified prior to the appearance of the disease (i.e. they are free of disease)***
- ***Study groups are observed over a period of time (follow-up)***
- ***Study proceeds forward from cause to effect***

Steps

1. Selection of study subjects

1. **General population**
2. **Special groups**
   i. Selected groups- doctors, teachers, lawyers
   ii. Exposure groups- industrial workers, radiologists

2. Obtaining data on exposure

i. Personal interviews
ii. Review of records
iii. Medical examination/ tests
iv. Environmental surveys

3. Selection of comparison groups

i. **Internal comparison**
   - according to degree of exposure
   - smoking

ii. **External comparison**
   - Cohart of radiologists with Cohart of ophthalmologists

4. Follow up

- Periodic medical examination
- Periodic home visit

5. Analysis

2×2 Table

	Disease present	Disease absent	Total
Exposure present	Exposed & developed disease (a)	Exposed but not developed disease(b)	Total exposed(a + b)
Exposure absent	Not exposed but developed disease(c)	Neither exposed nor developed disease(d)	Total non exposed(c + d)
Total	Total diseased (a + c)	Total non diseased (b + d)	Total study participants (a + b + c + d)

i. **Incidence rates**
- Among exposed = a/ a+ b
- Among non exposed = c/ c+ d

ii. **Estimation of risk (strength of association)**

a) ***Relative Risk*** **(*risk ratio*)**

$$RR = \frac{\text{incidence of disease among exposed}}{\text{incidence of disease among non exposed}}$$

- ***RR measures the strength of association between suspected cause & effect***

RR = 1 indicates no association
- Ex- smoking & HIV/ AIDS
- Interpretation- Chance of disease development is same among exposed as compared to non exposed

RR > 1 indicates positive association between exposure & disease
- Ex- smoking & lung cancer
- Interpretation- RR of _____ indicates that incidence of disease is _____ times higher in the exposed group as compared with unexposed

RR < 1 negative association between exposure & disease
- Ex- vitamin A intake & epithelial cancers
- Interpretation- -Chances of disease development is less among exposed as compared to non exposed Ex. RR of O.25 indicates 75 % reduction in incidence of disease in exposed as compared to unexposed

b) ***Attributable Risk***

$$AR = \frac{\text{incidence of disease among exposed - incidence of disease among non exposed}}{\text{incidence of disease among exposed}} \times 100$$

- Interpretation-_____so much of disease is attributed to exposure
- ***Good measure of extent of public health problem caused by the exposure***
- ***Most appropriate method to know about contribution of risk factors to disease***
- ***Assess etiological role or factor in disease***
- ***It is the risk difference between exposed & non exposed***
- ***Also known as absolute risk or excess risk or risk difference***

c) ***Population Attributable Risk***

$$PAR = \frac{\text{incidence of disease in total population} - \text{incidence of disease among non exposed}}{\text{incidence of disease in total population}} \times 100$$

- Interpretation- if risk factor is modified or eliminated, there will be so much_ annual reduction in incidence of disease in the given population
- ***PAR is the estimate of amount of disease that can be reduced if risk factor is modified / eliminated***
- ***Important measure for national health policy***

Utilities of Cohart Study
- Investigation of rare cause
- Testing multiple effects
- Measurement of time relationship
- Direct incidence measurement

Advantages of cohart study
- Incidence & Relative risk can be calculated
- No recall bias
- **Natural history of disease is best studied by cohart study**
- **Done for RARE CAUSE**
- **Useful for CHRONIC DISEASES**

Disadvantages of cohart study
- ***Unsuitable for RARE DISEASES***
- ***Expensive & time consuming***
- Loss to follow up

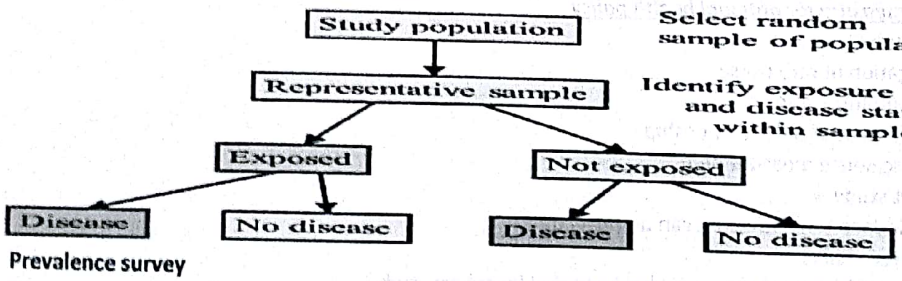
❖ Framingham Heart Study

- **Cohart study**
- 1948 by US public health services at Framingham
- To study relationship of risk factors (serum cholesterol, blood pressure, weight & smoking) & development of cardiovascular disease
- Age-group – 30-62 years
- Sample size- 5127
- Multiple exposure were studied by using multivariate methods
- Follow up- study population was examined every 2 years for 20 years
- **Findings of study**
  - Increasing risk of CHD with increasing **age** & more in **males**
  - **Hypertensive** have a greater risk of CHD
  - Elevated **blood cholesterol** associated with CHD
  - Tobacco **smoking** & habitual use of **alcohol** increases risk of CHD
  - Increase **body weight** predisposes CHD
  - **DM** increases risk of CHD
  - Increased **physical activity** decreases CHD development

6.3- Differences between Case control & Cohart study

	Case control study		Cohart study
i.	Proceeds from **effect to cause**	i.	Proceeds from **cause to effect**
ii.	Starts with the **disease**	ii.	Starts with the people **exposed**
iii.	Involves **fewer number** of subjects	iii.	Involves **larger number** of subjects
iv.	Yields **quick** results	iv.	Requires **long** follow up period
v.	Suitable for **rare diseases**	v.	Inappropriate for rare diseases
vi.	Estimates risk by **odds ratio**	vi.	Estimates risk by **Relative risk & Attributable risk**
vii.	Inexpensive	vii.	Expensive

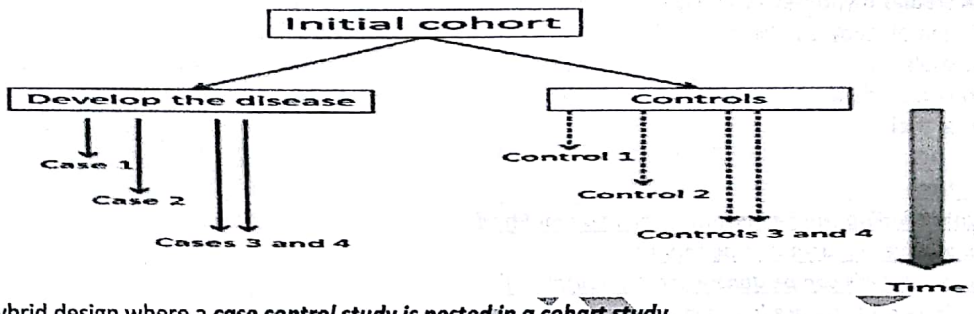
6.4 - Cross-Sectional Study



- **Prevalence survey**
- Exposure as well as outcome may coexist at the same time of study
- ***Based on single examination of a cross-section of population, at one point of time, result of sample are projected to whole population***
- Simplest form of observational epidemiological study
- ***Least time consuming study***

- **Advantages**
  - ***Gives a snapshot of a population***
  - ***Prevalence of a disease***
  - ***More useful for chronic diseases***
  - ***Show pattern of disease***
- **Disadvantages**
  - ***Tells about distribution of disease rather than its ETIOLOGY***
  - Cannot establish causality as does not establish time sequence

6.5- Nested Case Control Study



- Hybrid design where a ***case control study is nested in a cohart study***
- Predominantly a type of cohart study due to forward direction
- ***Limited for studies involving rare disease & whose diagnostic tests are very expensive***
- Only exposure has occurred when the study begins

Study design

- A population is identified & a base line data is obtained from interviews, blood or urine tests etc
- Population is than followed up for a period of time(cohart study) for development of diseases
- Case control study is then carried out
  - When the disease develops in a population, then 2 groups of cases(diseased) & controls (non-diseased) are formed & their exposure status is compared from the baseline data of history & collected samples
- ***Study design used for consanguineous marriage & genetic abnormalities***

Advantages

- ***Elimination of recall bias*** - as baseline information is taken at the start of study
- ***Maintenance of temporal association***
  - If any disease or abnormality in a biological characteristic is noted , it is more likely that it represents risk factors or other pre-morbid characteristics , rather than manifestation of early subclinical disease
  - ***As compared to routine case control study nested case control study avoids problem related to temporal association***

6.6- Ecological study

- **Correlational study**
- Provides least satisfactory type of evidence on causality
- Least preferable observational /analytical study design
- ***Unit of study is population***
- Uses data that is already available
- **Advantage**-- Provides group's characteristics
- **Disadvantage**- Socio economic confounding
  - **Ecological fallacy**- An error of interpretation in an ecological study , whereby characteristics are ascribed to a group of people which they may not possess as individual
- ***Examples of ecological study- In UK it was found that there were more deaths from asthma than the sale of anti asthma drugs***

6.7- Case Series Study

- Both outcome as well as exposure have occurred when the study has begun
- First we take outcome into consideration & then go back in time taking exposure into consideration
- There is no comparison with non diseased or controls
- ***Example – patients of glaucoma are identified & surveyed by patient interviews regarding family history of glaucoma***

7 - Experimental epidemiology

Experimental studies (hypothesis testing)

1. RCT (unit of study is patients)
2. Field trials
3. Community trials
4. Clinical trial

Experimental trials-

- ***Double blinding can be performed on in animal trial***
- ***Ethical issues on animal is debatable***
- ***Interim analysis can be done in experimental trial***
- ***Experimental trials are longitudinal & prospective***

Natural experiments

- ***If experimental studies not possible*** then natural circumstances can be used in human population that mimic an experimental study
- ***John snow cholera study is an experiment of natural experiment Study***
- ***Researcher has no control over allocation of subjects***
- Population that can be used- migrant population, religious group, population affected by nuclear disaster / natural disaster
- Used to study effects of intervention

7.1- Randomized Control Trial (RCT)

- ***Gold standard for clinical research is RCT***
- For new programmes & therapies RCT is the best method of evaluation
- ***Baseline characteristics of intervention are similar in both arms***
- ***Baseline characteristics are comparable***
- ***Investigator bias is minimized by double blinding***
- ***Sample size required depends on the hypothesis& type of study***
- ***The dropouts from the trial are not excluded from the study***
- ***Intention to retreat analysis is done in RCT***

Steps of RCT

1. ***Drawing up a protocol***
   - Specifies the aims & objectives of the study
   - Size of the sample
   - Treatment to be applied- when, where & to whom
2. **Selecting reference & experimental population**
   I. **Reference or target population**
      - It is the population to which the findings of the trial , if found successful, are expected to be applicable
      - May be geographically limited or limited to persons in specific age, sex, occupational or social groups

ii. **Experimental or study population**
   - Derived from the reference population
   - Actual population that participates in the study
   - It should be randomly chosen from the reference population
- ***Purpose of control group in an experimental study is that it helps to eliminate alternative explanations for the results of the study***

3. **Randomization**
- Statistical procedure by which the participants are allocated into groups called study & control groups to receive or not to receive the intervention
- ***Randomization is done while dividing patients into experimental group & reference group***
- ***Randomization is the heart of trial***
- Best done by using a table of random numbers

- **Purpose of randomization**
  - ***To equalize the effects of extraneous variables , thus guarding against bias***
  - Participants have equal & known chance of falling into either of the 2 groups
  - ***To eliminate selection bias***
  - ***To ensure comparability of 2 groups***
    - ***To ensure that study groups are comparable on baseline characteristics***
  - ***To have similar prognostic factor among 2 groups***
  - ***Facilitates blinding of treatment***
  - ***Increase internal validity of study***
- ***Random in randomization means equal & known chance***
- ***It is the heart of RCT***
- Randomization is better than matching as it removes both confounding & bias
  - Both known & unknown confounding factors are distributed equally among 2 groups thus nullifying their effect where as matching only useful for known confounding factors

  - ***Stratified randomization***
    - ***ideal to ensure similarity between experimental & control groups***
      - study population is first stratified by each important variable & than randomization is done to treatment groups within each stratum

4. **Manipulation or intervention**
- Deliberate application or removal of causal factor (e.g. drug, vaccine, habit etc.)

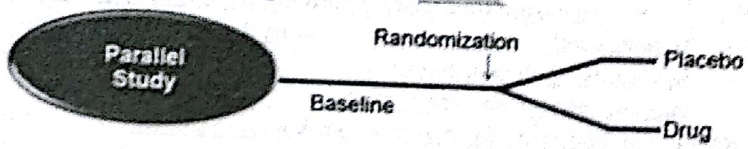
5. **Follow-up**
- Examination of the experimental & control group subjects at defined intervals of time with equal intensity, under the same given circumstances
- **Attrition**- some losses to follow up are inevitable due to factors , such as death, migration & loss of interest

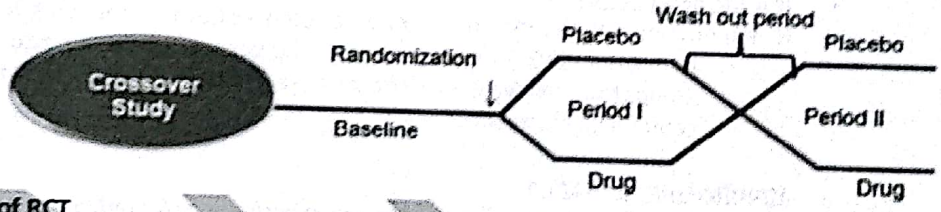
6. **Assessment of outcome**
- **Positive results**
  - Reduced incidence or severity of disease
- **Negative results**
  - Frequency of Side effects & complications

Study design

1. **Concurrent parallel study designs**
   - Comparison is made between 2 random groups
   - One group exposed to specific treatment (experiment group) & the other group not exposed (reference group)
   - Patient remains in the same group throughout the study duration
2. **Crossover type of study designs**
   - Each patient serves as his own control
   - Study group receives the treatment & control group receives the placebo
   - Patient in each group are taken off from their treatment or placebo to allow elimination of **carry over effects**
   - the two groups are now switched
   - Those who received treatment will receive placebo & those received placebo will now receive the treatment
   - ***Both groups acts as exposed as well as non exposed groups***
   - ***Cases acts as their own controls***
   - Helps in removing ethical concerns

- **Intention to treat trial** – result of RCT are unaffected by loss to follow up or changeover of study subjects from one group to another





3. **Types of RCT**
   - **Clinical trials**
     - Concerned with evaluating therapeutic agents , mainly drugs
     - E.g.- trial of aspirin on cardiovascular mortality
     - Should be carried out before any new therapy is introduced
   - **Preventive trials**
     - Trials of primary preventive measures
     - E.g.- trials of vaccines or chemoprophylactic drugs
   - **Risk factor trials**
     - Investigator interrupts the usual sequence in the development of disease for those individuals who have risk factors of disease
     - E.g.- multiple risk factor intervention trial (MRFIT) in USA
   - **Cessation experiments**
     - Attempt is made to evaluate the effect termination of habit or removal of agent & reduction of disease
   - **Trial of aetiological agents**
     - Aims to confirm or refuse an aetiological hypothesis
     - E.g.- trial for retrolental fibroplasia as a cause of blindness
   - **Evaluation of health services**
     - To assess the effectiveness & efficiency of health services
     - Also called health services research studies

7.2- Clinical Trials

- Does not have true control group- ***patients acts as their own control***
- Each patient has pre-test score followed by a post-test score

Clinical phase

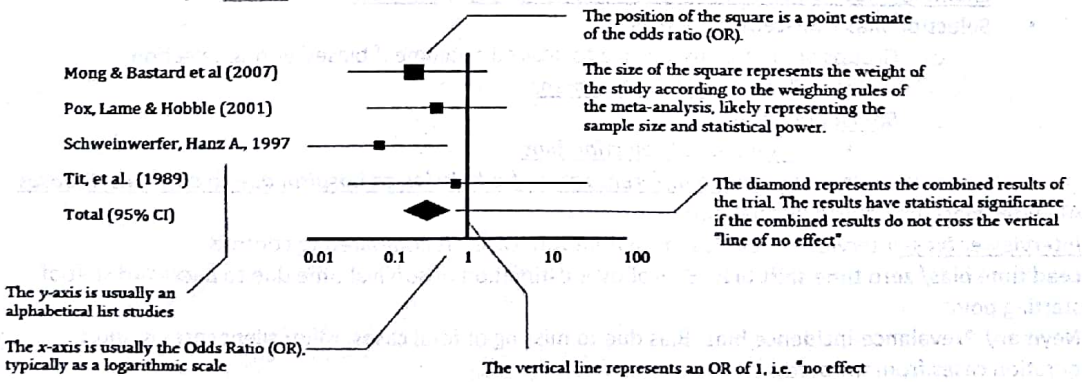
Phase	Units	Purpose
Preclinical phase		
Lab experiments	Animals	pretesting
Clinical phase		
Phase 0	Healthy humans volunteers	Micro-dosing
Phase I	***Healthy humans volunteers***	***Safety & non toxicity profile***
Phase II	Patients	Efficacy
Phase III	Patients	***Comparison with existing drug***
Phase IV	Patients	Long term & rare side effects

- ***Phase I- maximum tolerated dose of a drug is given & so evaluated in this phase***
- ***Phase II- maximum drug failure reported***
- ***Phase III***
  - ***It is an RCT*** as comparison of new drug is done with old drug
  - New drug is launched in market after phase III
- ***Phase IV***
  - Longest phase of a trial
  - ***Post marketing surveillance***

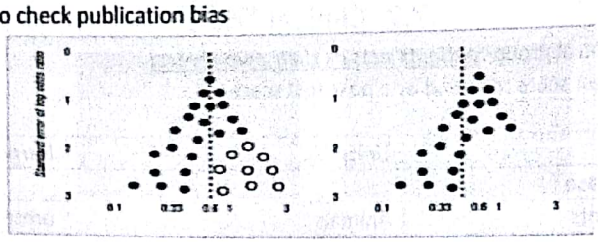
❖ ***When an intervention is applied to community to evaluate its usefulness, it is termed as a trial for effectiveness***

8- Meta- Analysis

- An objective & systematic review to combine & summarize the results of several studies
- Meant for summarizing large volume of data, determining the magnitude of an effect & to increase precision of studies
- ***Statistical technique for combining the finding from several independent studies on topic***
- ***Its purpose is not to identify risk factors but to increase statistical power by increasing sample size***
- ***Validity depends on the quality of systemic review***
- ***Metaanalysis can be embedded in systematic review but not always done in systematic review***
- Result-
  - **Forest plot**- to describe distribution of effect size



- **Funnel plot-** To check publication bias



No Publication Bias Publication Bias

- **Strength-**
  - Provide point estimate of effect size
  - Report confidence interval around effect size
  - Identify gaps in a particular field
- **Limitation**
  - **Garbage in Garbage out (GIGO)-** result can only be as good as the valid original data
  - **Apple & oranges effect-** tendency to mash together different effects
  - **File drawer effect-** publication bias

9- Bias

- Any systematic error in an epidemiological study, occurring during data collection, compilation, analysis & interpretation
- Arise from human errors of assessment of the outcome due to human element

1. **Subject bias**
   - Error introduced by study subjects
   - participants who may subjectively feel better if knew they were receiving a new treatment
   - **Attention bias / Hawthorne effect**
     - Study subject may systematically alter their behaviour when they know they are being watched
     - ***Seen in cohart study***
   - **Memory / *Recall bias***
     - Cases are more likely to remember exposure than controls
     - ***It is a systematic distortion of retrospective study that can be eliminated by a prospective design***
2. **Observer/ Investigator bias**
   - Investigator may be influenced if he knows beforehand that what therapy is given to which patient
   - ***Example- bias due to wrong interpretation of laboratory test***
   - **Selection bias / Susceptibility bias**
     - Groups are more susceptible to desired outcome if biased during selection
       - ***Occurs during recruitment***
     - ***Berksonian bias***
       - ***It is a type of selection bias***
       - ***It is due to different rates of admission to hospital due to different diseases***
3. **Analyzer bias-** Introduced by analyzer
4. ***Interviewer bias-*** Interviewer devotes more time with cases as compared to controls
5. **Lead time bias/ zero time shift bias-** Bias of over estimation of survival time due to backward shift of starting point
6. **Neyman/ Prevalance-incidence bias-** Bias due to missing of fetal cases. Mild/ silent cases & short duration cases from the study
7. **Bias in evaluation-** Investigator may subconsciously give a favorable report of the outcome of the trial

❖ ***Blinding, Randomization & Matching help to reduce bias***

10- Blinding

- Done in 3 ways
  1. ***Single blinding***
     - ***Participant is not aware whether he belongs to study group or control group***
     - Minimizes subject bias
  2. ***Double blinding***
     - ***Neither the investigator nor the participant is aware of the group allocation &the treatment received***
     - ***Minimizes*** subject bias & ***investigator bias***
     - Most frequently used method is double blinding
  3. **Triple blinding**
     - Participant, investigator & the person analyzing the data are all unaware of the two groups
     - Minimizes subject bias, investigator bias & analyzer bias
     - Ideally triple blinding should be used

11- Confounding

- Any factor viz associated with both exposure & outcome & has an independent effect in causation of outcome is a confounder
- ***Unequally distributed between study & control group***
- ***Associated with both exposure & outcome***
- ***Independent effect in causation of outcome***(so ***itself a risk factor)***
- ***Source of bias is interpretation***
- ***Methods used to control confounding***
  - ***Randomization***- most ideal method
  - ***Matching***- mostly useful in case control studies
  - **Restriction**
  - **Stratification**
  - **Statistical modeling**
  - ***Multivariate analysis***
- ***Example-***
  - ***A study revealed that lesser incidence of carcinoma colon in pure vegetarians than non vegetarians by which it was concluded that beta carotene is protective against cancer. This may not be true because the vegetarian subjects may be consuming high fibre diet which is protective against cancer***

11.1- Standardization of Death Rates

- While comparison of death rates of 2 population crude death rate (CDR) is not taken as age composition are different
- ***Standardized death rates are used for valid comparison of 2 groups of different health determinants***
- ***Standardization allows comparison between 2 different groups***
- Age standardization removes confounding effect of different age structures
- standardization is carried out by using standard population
- Standard population
  - population where age & sex group are known
  - ***national population need not always be taken as standard population***
  - used in occupational studies & for occurrence of diseases

Types of standardized death rates

- ***Direct Standardization***
  - ***Age specific death rates (ASDR)***
- ***Indirect Standardization***
  - ***Standardized mortality ratio (SMR)***

SMR = Observed death x 100
Expected death

- ***SMR is best to make a comparison between health status of 2 population***

❖ ***The rate adjusted to allow for the age distribution of the population is known as age standardized mortality rate***

❖ ***Standardized mortality rate is standardized for age***

❖ ***Specific death rates***

- ***Specific for age & sex***
- ***Identify at risk for preventive action***
- ***May be disease specific***

12- Matching

- Process of selecting controls in a such a way that they are similar to cases
- ***Matching is done to remove known confounding***
- Matching eliminates confounding as it distributes known confounding factors equally in 2 groups
- Types
  - **Caliper matching-** Matching of two groups within specified distance of a variable (matching age to within 2 years)
  - **Frequency matching-** Similar Frequency variable are matched between 2 groups
  - **Category matching-** Matching study & control groups in broad categories (example- similar occupation)
  - **Individual matching-** Identifying individual subject for comparison resembling a study subject for matched variable
  - **Pair matching-** Pair of study & comparison subjects are made

❖ Randomization is superior to both matching & blinding as it removes selection bias, known confounding & unknown confounding whereas matching removes only known confounding & blinding removes bias only

13- Association & Causation

Hills (surgeon general's) criteria of causal association

- ***Temporal association***
  - Cause preceded effect or effect follows cause
  - ***Suspected cause preceding the observed effect is an example for temporality***
  - Considers both order of appearance & length of interval between exposure & disease
  - ***Most important/ essential criterion of causal association***
  - Best established by a cohart study (especially concurrent cohart study)
- **Strength of association**
  - Relative risk (cohart study)- ***Cohart study is associated with antecedent causation***
  - Odds ratio (case control study)
- ***Specificity of association***
  - Implies that Disease is caused by risk factor
  - ***Most difficult criterion to establish***
  - Weakest criterion
- **Consistency of association-** results are replicable in different settings
- **Biological plausibility-** Credibility of association by anatomical/physiological justification
- **Coherence of association-** association is supported with relevant facts & studies
- **Dose response relationship-** increase in dose cause increase in incidence of effect
- ***Reversibility-*** removal of cause reduces risk of disease
  - ***Example- current smokers are at higher risk of developing lung cancer as compared to ex smokers***
- ***RCT are best studies for establishing causation***
- ***Ecological study is the weakest study to test the association between risk factor & disease***
- ***Indirect association – example- association of high altitude areas with goitre***

14- Uses of Epidemiology

1. **To study rise & fall of the disease**
   - Study of disease profiles & time trends in human population
2. **Community diagnosis**
   - Identification & quantification of health problems in a community in terms of mortality & morbidity rates & ratios
3. **Planning & evaluation of health services**
   - Epidemiological information about the distribution of health problems over time & place provides the fundamental basis for planning & developing the health services & for assessing the impact of these services
4. **Evaluation of individual risks**
   - Epidemiologists calculate relative risk & attributable risk for a factor related to be a cause of the disease
5. **Syndrome identification**
   - Medical syndromes are identified by observing frequently associated findings in individual patients
6. **Completing the natural history of disease**
   - Epidemiologists by studying disease patterns in the community in relation to agent, host & environmental factors is in a better position to fill up the gaps in the natural history of disease
7. **Searching for causes & risk factors**
   - Epidemiology , by relating disease to interpopulation differences & other attributes , tries to identify the causes of disease

15- International Death Certificate (IDC)

- 5 lines
  - **Line I.a**- condition directly leading to death
  - **Line I.b**- under lying cause
  - **Line I.c**- main underlying cause (if I.d is filled than that becomes main underlying cause)
  - **Line I.d**
  - **Line II**- other conditions contributing to deaths but not related to condition causing it
- ***Line I.c or I.d is the most important line in death certificate thus also known as essence of death certificate***

Example 1

- **Line I.a**- renal failure
- **Line I.b**- diaditic nephropathy
- **Line I.c**- Diabetes Mellitus
- **Line I.d**
- **Line II**- hypertension

Example 2

- **Line I.a**- intraperitonial hemorrhage
- **Line I.b**- ruptured metastatic deposits in liver
- **Line I.c**- metastatic deposits in liver
- **Line I.d**- primary adenocarcinoma of ascending colon
- **Line II**- hypertension